REMARKS/ARGUMENTS

Reconsideration of this application, as amended, is respectfully requested.

Claims 31-33 are pending in the present application.

Claims 31-33 have been rejected.

In the present response, claim 31 has been amended. Support for this amendment is in the present specification, as detailed below, and its entry is respectfully requested.

Claim 32 has also been amended to include the definitions of R' and R" which were inadvertently omitted from this claim. Support for this amendment is in the specification as filed at page 6, line 18, to page 7, line 2, and in U.S. Patent No. 5,491,172 (Lee et al.) (which, at page 3, lines 20-21, is incorporated by reference in the present application) at several places, including at column 25, claim 1, lines 21-25. No new matter is added to this application with this amendment, and its entry is respectfully requested.

The Examiner acknowledged Applicants' claims for domestic priority under 35 § U.S.C. 119(e) and 35 USC §§ 120 and/or 121. Also, the Examiner attached copies of the Applicants' Information Disclosure Statement, as initialed by the Examiner (Forms PTO-A820).

The Examiner noted that Applicant's amendment, filed August 12, 2003, was found persuasive and the following rejections have been withdrawn: (1) the rejection of claims 10, 21-21 and 27-36 under 35 USC § 112, first paragraph, for lack of enablement; (2) the rejection of claims 1, 10, 21-24 and 27 under 35 USC § 102(b) as being anticipated by Scolnick (WO 95/06470); and (3) the rejection of claims 1, 10, 21-24 and 27 under 35 USC § 102(b) as being anticipated by JP8143454.

CLAIM REJECTIONS – 35 USC § 112, FIRST PARAGRAPH

Claim 31 is rejected under 35 USC § 112, first paragraph, for scope of enablement because the specification, while being enabling for the particular compound of the formula in claims 32-33 herein employed in a method for treating Alzheimer's disease, allegedly does not reasonably provide enablement for the employment of any ACAT inhibitor to be administered for the claimed methods of the particular treatments herein in a patient. According to the Examiner, the recitation, "an ACAT inhibitor," in claim 31 is seen to be merely functional language. The Examiner alleged that, in view of the *In re Wands* factors,

the case *University of California v. Eli Lilly and Co.* (CAFC, 1997) and *In re Fisher* (CCPA 1970), to practice the claimed invention herein, a person of skill in the art would have to engage in *undue experimentation* to test all compounds encompassed in the instant claims and their combinations to be administered to a host employed in the claimed methods of the particular treatments herein, with no assurance of success.

As noted in Applicants' previous response, the term ACAT is well known in the art. As such, it is readily understood by those of skill in the art that an "ACAT inhibitor" is an inhibitor of acyl-coenzyme A:cholesterol acyltransferase. However, in order to expedite prosecution of the present application, claim 31 has been amended to include the meaning of the acronym "ACAT." Support for this amendment is in the specification as filed at page 6, lines 16-19. No new matter is added to the specification with this amendment; and its entry is respectfully requested.

Furthermore, in the specification as filed, at page 6, line 16, to page 7, line 5, Applicants have shown that ACAT inhibitors are well known in the art and have provided representative examples of ACAT inhibitors, such as in U.S. Patent No. 5,491,172 (Lee et al.). In addition, assays that measure the ability of a compound to inhibit ACAT are also well known in the art. For example, the Lee et al. patent (which is incorporated by reference in the present application, at page 3, lines 20-21) references such an assay at column 7, lines 34-42.

Also, in the present specification, as filed, Applicants have provided support for the use of ACAT inhibitors in the methods of the present invention with the description of the hosts, dosages and modes of administration (see the present specification at page 9, lines 1-26). Applicants have also provided a description of the relevant assays and animal models for Alzheimer's disease with supporting data at page 9, line 27, to page 18, and as further described below. Therefore, Applicants assert that they have provided enabling support for claim 31 of the present application.

Applicants would also note that the Examiner has stated that the specification provides no working examples, i.e., testing results or data demonstrating that any ACAT inhibitors to be administered to a human, are capable of treating Alzheimer's disease in a patient.

In response, Applicants would point out that the courts have repeatedly made it clear that the PTO is not the Food and Drug Administration ("FDA"). The only question

for the PTO regarding utility is: Is the invention useful? It is for the FDA to determine if human testing is required or even appropriate, with completely different considerations than patentability. MPEP section 2107.03 (subsection IV) states that office personnel should not impose on applicants the unnecessary burden of providing evidence from human clinical trials. It continues, stating that there is no decisional law that requires an applicant to provide data from human clinical trials to establish utility for an invention related to treatment of human disorders.

Also, Applicants would disagree with the Examiner's comment that there is no working examples, i.e., testing results or data in the present specification, as filed. Applicants have included data from well-recognized human and animal models in the specification as filed, for example, in the following: Example 1 and Table 1 (pages 10-16) and accompanying Figures 1, 2, 3 and 4; Example 2 (page 16, line 1, to page 17, line 10) and accompanying Figures 5 and 6; and Example 3 (page 17, line 11, to page 18) and accompanying Figure 7.

As noted in Applicants' previous response, β-amyloid (Aβ) is the principal proteinaceous component of amyloid associated with Alzheimer's disease (AD). Aβ is viewed as a likely underlying cause of the degeneration and dementia that characterizes AD. Applicants' disclosure shows that total cholesterol and LDL cholesterol are correlated with levels of β-amyloid (Example 1, page 14, lines 3-24, and accompanying Figures). In addition, Applicants' disclosure shows that both statins and ACAT inhibitors lower Aβ in Chinese Hamster Ovary (CHO) cells that have been engineered to over-express human β-amyloid precursor protein (Example 2, page16). Applicants have also shown that, consistent with these CHO data, levels of Aβ in the brains of animals are reduced in response to treatment with simvastatin (Example 3, page 17). Applicants' data in the specification as filed provides support for the conclusion that ACAT inhibitors are useful for the treatment of AD.

In addition, in a recent Abstract, which was published in November of 2003, it was shown that an ACAT inhibitor reduced insoluble brain A^{β} levels in a transgenic mouse model of Alzheimer's disease. The Abstract provides further support for Applicants' invention that ACAT inhibitors are useful for treating Alzheimer's Disease. A copy of this Abstract (D.M. Kovacs et al., "ACAT inhibition reduces insoluble brain A^{β} levels in a transgenic mouse model of Alzheimer's disease," Program No. 336.7; 2003 *Abstract*

Viewer/Itinerary Planner; Washington, DC: Society for Neuroscience) is included herewith for the Examiner's reference.

Therefore, with the above amendment and the enabling disclosure, Applicants respectfully request that this rejection of claim 31, as amended, under 35 USC § 112, first paragraph, be withdrawn.

CLAIM REJECTIONS – 35 USC § 112, SECOND PARAGRAPH

Claim 33 is rejected under 35 USC § 112, second paragraph, for "indefinite expressions the name ACAT for reasons of record stated in the Office Action dated February 12, 2003." According to the Examiner, Applicant's remarks in Paper No. 8 with respect to this rejection have been fully considered but are not deemed persuasive since as noted in MPEP 2111, during patent examination, claims are given their broadest reasonable interpretation. The Examiner concluded that in the instant case, the expression "ACAT inhibitors" used to identify/describe particular compounds herein and, accordingly, the identification/description is indefinite.

As noted above, in order to expedite prosecution of the present application, claim 31 has been amended to include the meaning of the acronym "ACAT." Claim 33 depends from claim 31, and, thus, it includes this meaning as well. Therefore, Applicants respectfully request that this rejection of claim 33, as amended, under 35 U.S.C. §112, second paragraph, be withdrawn.

CLAIM REJECTIONS – 35 USC §103

Claims 31-33 are rejected under 35 USC § 103(a) as being unpatentable over Lee et al. (U.S. 5,491,172, of record) in view of Scolnick (WO 95/06470, of record) for reasons of record stated in the Office Action dated February 12, 2003. The Examiner alleged that the claimed invention as a whole is prima facie obvious over the combined teachings of the prior art.

As noted in Applicants' previous response, Lee discloses a genus of ACAT inhibitors and their utility for treating hypercholesterolemia and atherosclerosis. As acknowledged by the Examiner, Lee does not "disclose that the instant claimed compound may be useful in a method of treating Alzheimer's disease." There is no mention of Alzheimer's disease in the Lee reference.

Scolnick discloses that HMG-CoA reductase inhibitors (lovastatin, simvastatin, pravastatin and fluvastatin) may be useful to lower Apolipoprotein E isoform 4 (Apo E4) to treat and prevent Alzheimer's disease. Scolnick does not disclose or discuss the use of ACAT inhibitors in the treatment of Alzheimer's disease (AD).

For the reasons given in their previous response, Applicants respectfully assert that it would not have been obvious to one skilled in the art, in view of Lee and Scolnick, that ACAT inhibitors would be useful in the treatment of Alzheimer's disease. There was no motivation in either Lee or Scolnick to substitute ACAT inhibitors in the methods of Scolnick to arrive at the presently claimed invention. This is especially true because of the very different mechanisms of action by which statins and ACAT inhibitors operate (as explained in detail in Applicants' previous response). Even if there were motivation to combine the references, there would not have been a reasonable expectation of success that ACAT inhibitors would be useful for the treatment of Alzheimer's Disease. It is the present application that is the first disclosure that ACAT inhibitors do indeed have that utility.

The Examiner noted that Applicant's remarks filed on August 12, 2003 in Paper No. 8 with respect to this rejection made under 35 USC § 103(a) of record in the previous Office Action have been fully considered but are not deemed to be persuasive. The Examiner noted, as discussed above in the rejection under 35 USC § 112, first paragraph, that the specification provides no working examples, i.e., testing results or data demonstrating that any ACAT inhibitor to be administered to a human are capable of treating Alzheimer's disease in a patient. Therefore, the Examiner alleged that there is no clear and convincing evidence of nonobviousness or unexpected results in the specification herein in support of the nonobviousness of the instant claimed invention over the prior art.

As explained above and in Applicants' previous response, the Examiner has not established a *prima facie* case of obviousness of the present application, in light of the prior art references; therefore, no evidence of nonobviousness or unexpected results is required. Furthermore, it is for the FDA, not the PTO, to determine if human testing is required or even appropriate. Also, from the present specification as filed and the current literature, Applicants have provided data from well-recognized models for Alzheimer's Disease in support of their invention that ACAT inhibitors are useful for treating Alzheimer's Disease.

Therefore, Applicants submit that claims 31-33, as amended, are patentable over the Lee and Scolnick references, either singly or in combination, and respectfully request that

this rejection of the claims under 35 USC § 103 be withdrawn.

On the basis of the above amendments and remarks, reconsideration of this application, as amended, and its early allowance, are respectfully requested.

Respectfully submitted,

Date: May 4, 2004

Martha A. Gammill
Attorney for Applicants
Reg. No. 31,820
Pfizer Inc.
Patent Department
2800 Plymouth Road
Ann Arbor, MI 48105
Tel. (734) 622-5940
Fax (734) 622-1553

Attachments:
Petition for Extension of Time Form
Associate Power of Attorney Form
Copy of Abstract: D.M. Kovacs et al., "ACAT inhibition reduces insoluble brain A^{β} levels in a transgenic mouse model of Alzheimer's disease," Program No. 336.7; 2003 *Abstract Viewer/Itinerary Planner*; Washington, DC: Society for Neuroscience

Program Numb r: 336.7 **Day / Time:** Monday, Nov. 10, 9:30 AM - 9:45 AM

ACAT inhibition reduces insoluble brain Aβ levels in a transgenic mouse model of Alzheimer's disease.

D.M.Kovacs ; M.P.Frosch; S.Domnitz; L.Puglielli

Dept. of Neurol., Massachusetts Gen. Hosp., Harvard Med. Sch., Charlestown, MA, USA

Mounting evidence indicates that fine imbalances in intracellular cholesterol distribution to lipid rafts, the Niemann-Pick C1 compartment, and cholesteryl-ester droplets can trigger changes in amyloid β-protein (Aβ) generation. One class of compounds, acyl CoA:cholesterol acyltransferase (ACAT) inhibitors, reduce cholesteryl-ester generation and also lower Aβ production in cells (Puglielli et al., 2001). 21-day time-release pellets of an ACAT inhibitor, CP113,818 (Pfizer), implanted into 3-month old non-transgenic mice reduced hepatic and brain cholesteryl-esters levels by 93% and 86%, respectively, while not inducing any apparent toxic effects. We used a transgenic mouse model of Alzheimer's disease (AD) to assessthe impact of CP113,818 on brain Aβ accumulation and cognitive impairment. In this model, expression of the human amyloid precursor protein (APP) harboring the Swedish and London mutations, driven by the murine Thy-1 promoter, results in amyloid plaque deposition and behavioral deficits at 4 and 6 months of age, respectively. 60-day time-release pellets of CP113,818 decreased insoluble brain $Aβ_{40}$ and $Aβ_{42}$ levels by 70-90% at 7 months of age, however, Aβ ratios were unaffected. Learning, as shown in a Morris water maze test, indicated a trend for improvement, but was not statistically significant. Preliminary studies in a PS1(M146L)/APP(Swedish) double transgenic mouse model confirmed a significant reduction of Aβ levels in insoluble mouse brain extracts. The mechanism by which ACAT inhibitors reduce Aβ production requires a novel cleavage in the N-terminal domain of APP that antagonizes secretase cleavage of APP. Mechanistic studies in concert with studies carried out on transgenic animal models are the first essential steps in developing ACAT inhibitors as potential therapeutic agents for the treatment and prevention of AD.

Support Contributed By: the NIH/NINDS and the Institute for The Study of Aging (ISOA)

Citation: D.M.Kovacs, M.P.Frosch, S.Domnitz, L.Puglielli. ACAT inhibition reduces insoluble brain Aβ levels in a transgenic mouse model of Alzheimer's disease.. Program No. 336.7. *2003 Abstract Viewer/Itinerary Planner.* Washington, DC: Society for Neuroscience